REMARKS

Reconsideration of this application is respectfully requested.

Claims 56-61, 78-80, 82, 84, 89-94, and 98-114 have been canceled. Claims 115-158 are new.

Upon amendment, claims 62-77, 81, 83, 85-88, 95-97, and 115-158 are pending in the application, with claims 62-77, 81, 83, 85-88, and 95-97 withdrawn from consideration.

Support for new claims 115-158 can be found throughout the specification, for example, as follows:

Claim	Support
115	Original claim 3.
116	Original claims 4-5; figure 1c; page 15, SEQ ID NO: 14, SEQ ID NO: 16, and SEQ ID NOS: 18-22.
117	Original claim 3; page 20, ll. 10-17.
118	Original claims 4; original claim 6, figure 1c.
119	Page 16, ll. 1-7; page 18, ll. 12-15.
120	Original claim 4; original claim 6; page 20, ll. 10-17.
121	Page 16, ll. 1-7.
122	Figure 1b; page 15, SEQ ID NOS: 7-9; page 13, ll. 18-22.
123	Figure 1b; page 15, SEQ ID NOS: 7-9; page 13, ll. 18-22.
124	Figure 1b; page 15, SEQ ID NO: 7 and SEQ ID NO: 9; page 13, ll. 18-22.
125	Figure 1b; page 15, SEQ ID NOS: 7-9; page 13, ll. 18-22.
126	Page 13, ll. 18-22; figure 1b; page 15, SEQ ID NO: 9.
127	Figure 1b; page 15, SEQ ID NO: 9.
128	Original claim 8; original claim 9; figure 1b; page 15, SEQ ID NOS: 7-9; page 13, ll. 18-22.
129	Page 18, ll. 10-11, page 15, SEQ ID NOS: 7-9.
130	Page 20, ll. 10-17, page 15, SEQ ID NOS: 7-9.
131	Original claim 8; original claim 9; figure 1b; page 13, ll. 18-22; page 20, ll. 10-17.
132	Page 26, ll. 9-15.
133	Page 4, ll. 16-20; original claim 7.
134	Figure 1b; page 15, SEQ ID NOS: 7-9; page 13, ll. 18-22.

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Claim	Support
135	Page 4, ll. 11-21.
136	Page 4, ll. 2-10, original claim 1; original claim 2.
137	Page 4, ll. 12-15; figure 1c; page 15, SEQ ID NO: 14, SEQ ID NO: 16, and SEQ ID NOS: 18-22.
138	Page 4, ll. 12-15; figure 1c; page 20, ll. 10-17.
139	Page 18, ll. 12-15.
140	Page 4, ll. 2-10.
141	Figure 1b; page 15, SEQ ID NOS: 7-9; page 13, ll. 18-22.
142	Page 4, l. 22 - page 5, l. 2; figure 1b, page 15.
143	Page 4, l. 22 - page 5, l. 2; figure 1b; page 15, SEQ ID NO: 7 and SEQ ID NO: 9.
144	Figure 1b; page 15, SEQ ID NOS: 7-9; page 13, ll. 18-22.
145	Figure 1b; page 15, SEQ ID NO: 9.
146	Figure 1b; page 15, SEQ ID NO: 9; page 13, ll. 18-22.
147	Page 4, l. 22 - page 5, l. 2; figure 1b, page 15; page 20, ll. 10-17.
148	Page 18, ll. 10-11.
149	Page 13, ll. 18-24; figure 1c; page 15, SEQ ID NO: 14, SEQ ID NO: 16; and SEQ ID NOS: 18-22.
150	Page 16, ll. 1-7; page 18 ll. 12-15.
151	Page 13, ll. 18-24; figure 1c; page 15, SEQ ID NO: 14, SEQ ID NO: 16; and SEQ ID NOS: 18-22; page 20, ll. 10-17.
152	Page 13, ll. 18-24; figure 1b; page 15, SEQ ID NO: 7 and SEQ ID NO: 9.
153	Page 13, ll. 18-24; figure 1b; page 15, SEQ ID NO: 7 and SEQ ID NO: 9.
154	Page 13, ll. 18-24; figure 1b; page 18, ll. 10-11.
155	Page 13, ll. 18-24; figure 1b; page 20, ll. 10-17.
156	Page 13, ll. 18-24; figure 1b; page 15, SEQ ID NO: 9.
157	Page 13, ll. 18-24; figure 1b; page 15, SEQ ID NO: 9.
158	Page 13, ll. 18-24; figure 1b; page 15, SEQ ID NO: 9.

Applicants submit that these claim amendments are fully supported by the specification, do not introduce new matter or require a further search of the art, and respectfully request their entry.

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Filing Date

Applicants note that the filing date printed on Paper No. 17 is 9/10/2001. This is not correct. The filing receipt and corrected filing receipt both list the correct filing date, 5/16/01 (Exhibit 1). Applicants respectfully request that the Examiner verify the accuracy of the filing date, and have it corrected in the Patent Office Records.

Background

In the instant application, Applicants sequenced the pertactin repeated regions of 10 *B. parapertussis* isolates and 40 *B. bronchiseptica* isolates. No difference was found between the repeated regions of the 10 *B. parapertussis* isolates and the published sequence. However, variability in the number and type of repeat sequences was observed in the two repeated regions of *B. bronchiseptica*: for example, the number of GGAVP repeats in Region I varies from 1 to 3, and the number of PQP repeats in Region II varies from 6 to 9. (Figure 1b.)

Claim Objections

The Office objected to the use of "numerous abbreviations" in claims 89-94 and 109-114.

Applicants have incorporated the full length name of each abbreviation into new claims 115-158. Accordingly, the objection is now moot.

Additionally, the Office objected to the term "where in the adhesin" in claims 89-94 and 109-114, suggesting instead the term "wherein the adhesin". New claims 117, 120, 130, 138, 147, 151, and 155 incorporate the suggested phrase.

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Claim Rejections under 35 U.S.C. § 112, First Paragraph, Enablement

The Office rejected claims 82 and 84 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled for a pharmaceutical composition. The Office contended that it is well recognized in the art that it is unclear whether a single protein derived from a pathogen will elicit protective immunity. (Office Action at Item 4.) Although Applicants believe that the specification enables a pharmaceutical composition, Applicants have adopted the language suggested by the Examiner in an effort to facilitate prosecution. As such, new claims 131 and 132, which are derived from rejected claims 82 and 84, remove explicit reference to a vaccine or a vaccination kit, instead reciting "An immunogenic composition. . ." or "A kit comprising an immunogenic composition. . . ." Applicants note, however, that the immunogenic composition may have a protective effect when used *in vivo*, because an immunogenic composition by definition elicits an immune response. Applicants thus respectfully request the withdrawal of the 35 U.S.C. § 112, first paragraph, enablement rejection.

Claim Rejections under 35 U.S.C. § 112, First Paragraph, Written Description

The Office rejected claims 56-61, 78-80, 82, 84, 89-94, and 98-114 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description support. (Office Action at Item 5.) The Office stated, in pertinent part:

> Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the fragment of the pertactin represented by SEQ ID NO: 8 alone is insufficient to describe the genus. Thus, Applicants have not described a function which is shared by SEQ ID NO: 8 which would adequately describe the genus. One of skill in the art would

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> reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus. It is further noted that SEQ ID NO: 8 is not a full length protein, given that the classical start codon, methionine is absent. Given that the function of the non-full length protein is not set forth, the written description of the instant application is supportive of only an antigenic peptide consisting of SEQ ID NO: 8, since additional amino acids on the N-terminus or C-terminus will have a profound impact on the activity of the protein.

Applicants are confused about the genus allegedly represented only by SEQ ID NO: 8. In Item 1 of the May 23, 2003, Office Action (Paper No. 17), the Office waived the restriction to a single sequence, agreeing to examine all of the sequences disclosed in the instant application. Applicants have provided full length pertactin sequences for *Bordetella bronchiseptica*, *Bordetella parapertussis*, and *Bordetella pertussis*, including SEQ ID NOS: 4-6. Thus, in contrast to the allegations of the Office, full length protein sequences were fully and precisely described.

Additionally, Applicants have provided the sequence of pertactin variants with, for example, 1, 2, or 3 GGAVP amino acid sequences in Region I, as well as pertactin variants with 6, 7, 8 or 9 PQP sequences in Region II. (Page 15, SEQ ID NOS: 7-24.) Thus, Applicants describe variants containing various numbers of repeating sequences in Region I and Region II.

Additionally, Applicants respectfully traverse the specific assertions made by the Office in the paragraph quoted above regarding the disclosure of the instant application.

First, the Office alleged that SEQ ID NO: 8 does not describe "a function which is shared" by members of the genus. (Office Action at Item 5.) However, the rejected

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claims are drawn toward an "immunogenic composition," and the specification describes functions for this immunogenic composition. A partial list of these functions includes: protection against *Bordetella* infection, treatment of subjects infected with *Bordetella*, and diagnosis of *Bordetella* infection. (Page 3, ll. 20-24.) As such, it is clear that Applicants have amply described the shared function of the genus.

Second, the Office alleged that "because the function of the non-full length protein is not set forth, the written description of the instant application is supportive of only an antigenic peptide consisting of SEQ ID NO: 8, since additional amino acids on the N-terminus or C-terminus will have a profound impact on the activity of the protein." (Office Action at Item 5.) Applicants respectfully traverse. As stated previously, multiple full-length pertactin sequences are provided. Moreover, the claims in the instant invention are drawn toward an immunogenic composition - that is, a composition sufficient to induce a humoral or cellular immune response against *Bordetella* species in an animal to which the composition is administered. (*See, e.g.*, page 4, ll. 1-9.) It is well known that a protein fragment, and even a short amino acid peptide, can act as an immunogen, and Region II has already been identified as an immunodominant epitope. (Antibodies, a Laboratory Manual at pages 72-73; page 2, ll. 21-23; Exhibit 2.) Thus, whether or not the mixture of immunogenic pertactins comprises full-length pertactins or pertactin fragments is irrelevant, because both serve to elicit an immune response.

Applicants submit that the Office has not met its burden of "presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims." M.P.E.P. § 2163. Given the disclosure of multiple full-length sequences and the abundance of sequence variants

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provided, Applicants submit that the 35 U.S.C. § 112, first paragraph, written description rejection is not applicable to new claims 115-158.

Claim Rejections under 35 U.S.C. § 102(b)

The Office rejected claims 56-61, 78-80, 82, 84, and 98-103 under 35 U.S.C. § 102(b) as being anticipated by Charles et al. (WO 92/11292). In particular, the Office alleged that Charles et al. anticipates the "mixture of pertactins of *Bordetella* species, fragments and variants thereof, wherein the composition comprises at least one of: pertactins of *B. bronchiseptica*, pertactins of *B. parapertussis*; and pertactins of *B. pertussis*. . . ." (Office Action at Item 6.)

Applicants submit that new claims 115-158 are not anticipated by Charles et al. Charles et al. disclose the isolation and purification of a pertactin from *Bordetella parapertussis*, as well as its incorporation into a vaccine. Charles et al. further state, "The vaccine of the invention may optionally contain additional antigens of *B. parapertussis* or other bacteria, such as *B. pertussis*, tetanus and diptheria." (Charles et al. at page 8, lines 4-6.) In other words, Charles et al. disclose a vaccine consisting of a *B. parapertussis* pertactin along with *any other antigen from any other bacteria*, a genus of essentially unlimited scope, suggesting such unrelated species and antigens as *B. pertussis*, tetanus, and diptheria.

Because the genus of Charles et al. is essentially unlimited (including any antigen from any bacteria), this genus fails to "identically disclose or describe within the meaning of section 102" the claimed sub-genus, "since the genus would include an untold number of species." *See In re Meyer*, 599 F.2d 1026, 1031, 202 U.S.P.Q. 175,

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179 (C.C.P.A. 1979). Claims 115-148 recite a mixture of *Bordetella* pertactins or pertactin fragments. Because Charles et al. provides no direction toward selecting a mixture of pertactins or pertactin fragments of *Bordetella* species, it does not teach every element of claims 115-148 and cannot anticipate the claims. *See* M.P.E.P. § 2131.

Furthermore, new claims 115-134 recite an immunogenic composition comprising a mixture of *Bordetella bronchiseptica* pertactins or pertactin fragments, and new claims 149-158 recite an immunogenic composition comprising a purified *Bordetella bronchiseptica* pertactin or pertactin fragment. Because Charles et al. does not teach a *Bordetella bronchiseptica* pertactin / pertactin fragment or a mixture of *Bordetella bronchiseptica* pertactins / pertactin fragments, Charles et al. cannot anticipate new claims 115-134 and 149-158. *See* M.P.E.P. § 2131.

The Office also rejected claims 56-61, 78-80, 82, 84, and 98-108 under 35 U.S.C. § 102(b) as being anticipated by Clare et al. (WO 91/15571). (Office Action at Item 7.)

Applicants submit that new claims 115-158 are not anticipated by Clare et al. Clare et al. disclose a vaccine containing recombinant *B. pertussis* pertactin expressed and purified in the yeast *Pichia pastoris*. (*See*, for example, abstract and page 15.) Clare et al. state that their recombinant pertactin is free of "contaminating *B. pertussis* antigens," emphasizing that a single pertactin variant from a single species is provided. In contrast, new claims 115-134 recite an immunogenic composition comprising a mixture of *Bordetella bronchiseptica* pertactins or pertactin fragments, new claims 135-148 recite an immunogenic composition comprising a mixture of pertactins or pertactin

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fragments of *Bordetella bronchiseptica*, *Bordetella parapertussis*, or *Bordetella pertussis*, and new claims 149-158 recite an immunogenic composition comprising a *Bordetella bronchiseptica* pertactin or pertactin fragment.

Clare et al. does not teach the use of a pertactin or pertactin fragment from *Bordetella bronchiseptica*, and does not teach a mixture of pertactins or pertactin fragments. Since Clare et al. discloses only a single pertactin from *B. pertussis* in an immunogenic composition, it does not contain all the elements of these claims, and cannot anticipate them. M.P.E.P. § 2131.01; *Verdegaal Bros. v. Union Oil. Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q. 2d 1051, 1053 (Fed. Cir. 1987); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986).

Claim Rejections under 35 U.S.C. § 103(a)

Claims 56-61, 78-80, 82, 84, 89-94, and 98-114 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Charles et al. or Clare et al. in view of Gueirard et al. (Office Action at Item 8.)

As discussed previously, Charles et al. and Clare et al. do not disclose a mixture of *Bordetella* pertactins / pertactin fragments in an immunogenic composition (claims 115-148), or the use of *B. bronchiseptica* pertactins / pertactin fragments (claims 115-134 and claims 149-157) in an immunogenic composition. Gueirard et al. do not remedy these deficiencies. Accordingly, Applicants respectfully request withdrawal of this rejection.

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In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
09/855,754	05/16/2001	1643	0.00	03495.0206	1	55	17

CONFIRMATION NO. 8881

CORRECTED FILING RECEIPT

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Nicole Guiso-Maclouf, Residence Not Provided;

Domestic Priority data as claimed by applicant

THIS APPLN CLAIMS BENEFIT OF 60/206,969 05/25/2000

Foreign Applications

If Required, Foreign Filing License Granted 06/11/2001

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No

Title

Polypeptides containing polymorphisms of the repeated regions of pertactin bordetella pertussis, bordetella parapertussis, and bordetella bronchiseptica, their use in diagnostics, and in immunogenic compositions

Preliminary Class

435

Data ntry by : DOUGLAS, BRIDGETTE Team : OIPE Dat : 06/29/2001

KJM

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APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
09/855,754	05/16/2001	1643	0.00	03495.0206	1	55	17

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JUN 13 2001

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Nicole Guiso-Macouf, Residence Not Provided;

Domestic Priority data as claimed by applicant

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Polypeptides containing polymorphisms of the repeated regions of pertactin bordetella pertussis, bordetella parapertussis, and bordetella bronchiseptica, their use in diagnostics, and in immunogenic compositions

6/13/01

Preliminary Class

435

Data entry by : KELECHA, ASEGEDECH **Team :** OIPE **Date:** 06/11/2001

Haptens

Many small chemicals can be used to raise antibodies, if they are coupled to larger protein molecules. The small compounds are known as haptens, while the proteins to which they are coupled to are called carriers. The haptens themselves serve as epitopes for binding to the antibodies on the B-cell surface, and the carriers provide the class II–T-cell receptor binding sites. In general, haptens should be coupled to soluble carriers such as bovine serum albumin (BSA) or keyhole limpet hemacyanin (KLH). The coupling mechanism will vary with each hapten, but many of the bifunctional coupling reagents listed in Table 5.5 (p. 130) will be helpful. Also, the techniques on the coupling of synthetic peptides to carriers on p. 78 may be applied. In general, approximately 1 mole of hapten per 50 amino acids of carrier is a reasonable coupling ratio.

Synthetic Peptides

The use of synthetic peptides as immunogens has been an important technique in the elucidation of the properties of an antibody response (e.g., Goebel 1938; Anderer 1963; Anderer and Schlumberger 1965; Sela 1966, 1969; Arnon et al. 1971). Recently, as more DNA sequences

Choosing between Bacterial Expression and Peptides for Immunogen Production

When a cloned DNA sequence in available, antibodies can be prepared either using peptides or bacterially expressed proteins. There are strong proponents for both approaches, both groups citing their experiences favoring one method over the other. Both have advantages and disadvantages, and for a particular antigen one may be better suited than another. However, if both approaches are available to a researcher, both should be used.

For anti-peptide antibodies, a good response to the desired peptide usually can be generated with careful selection of the sequence and coupling method. Because of the way in which the peptide is displayed to the immune system, most peptides elicit a good response. Therefore, the anti-peptide approach has major advantages if the antigen is known to be highly conserved. Likewise, if antibodies need to be raised against a particular region, anti-peptide antibodies have many advantages. The major disadvantage with anti-peptide antibodies is that they may not recognize the native antigen. The percentage of antibodies raised against peptides that will bind to the native protein will vary from antigen to antigen. Values reported in the

and their corresponding protein sequences have become known, synthetic peptides have been used to prepare antibodies specific for previously uncharacterized proteins (Sutcliffe et al. 1980; Walter et al. 1980; and reviewed in Lerner 1982, 1984; Walter 1986; Doolittle 1976; and in Ciba Foundation 1986). Peptides are normally synthesized using the solid-phase techniques pioneered by Merrifield (1963). The synthetic peptides are purified and coupled to carrier proteins, and these conjugates are then used to immunize animals. In these cases, the peptides serve as haptens with the carrier proteins, providing good sites for class II–T-cell receptor binding. Peptide–carrier conjugates seldom fail to elicit a response because of tolerance. Consequently, the peptides can usually be seen as epitopes, and high-titered antisera commonly are prepared. Characteristically, these antibodies will bind well to denatured proteins, but may or may not recognize the native protein.

The two most important advantages of anti-peptide antibodies are that they can be prepared immediately after determining the amino acid sequence of a protein (either from protein sequencing or from DNA sequencing) and that particular regions of a protein can be targeted specifically for antibody production. Rapid conversion from DNA sequence information to antibodies has enormous potential for application in molecular biology. Similarly, the production of site-specific antibodies has immediate implications for functional and clinical studies.

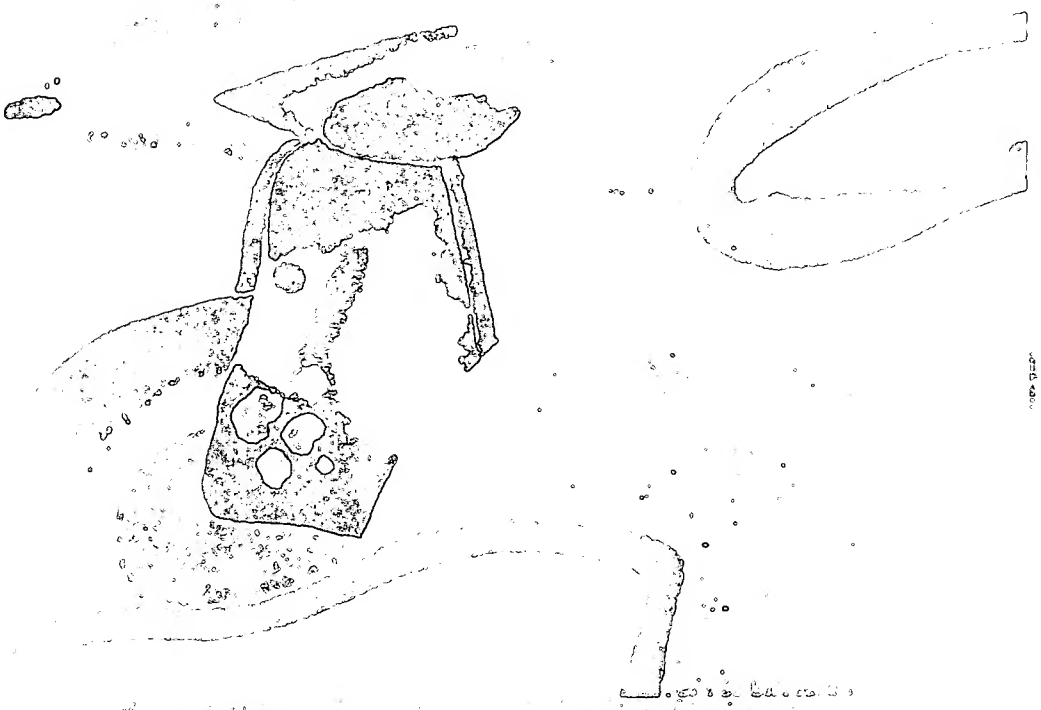
literature range from 0/4 to 3/4 of anti-peptide antibodies will bind to the native antigen. Synthetic peptide antigens are also more expensive to produce than bacterial fusion protein antigens.

Bacterially expressed antigens present a different set of problems. Some will be difficult to express in *E. coli*, presumably because of their toxic side effects. In these cases, inducible systems such as the T7 systems of Studier (see Rosenberg 1987; Studier and Moffatt 1986) are recommended. Even when high levels of the antigen of interest can be produced, there may be some instances where the protein will not be immunogenic or where the antibodies will not recognize the native protein. However, because of the larger size of the bacterially expressed protein, there is a better chance that the antibodies will bind to the native protein.

A reasonable compromise for antibody production would be: (1) If the budget is limited and/or antibodies for the native protein are essential, use fusion proteins or full-length expression in *E. coli*. (2) If the budget is large enough, try both bacterially produced immunogens and peptides. (3) If the protein is highly conserved, use peptides. (4) If site-directed antibodies are needed, use peptides or prepare large banks of monoclonal antibodies against the bacterially produced immunogens.

Antibodies

A LABORATORY MANUAL



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Antibodies

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1988